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Value of Digoxin in Heart Failure and Sinus Rhythm: New Features of an Old Drug?

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Digoxin has been a controversial drug since its introduction >200 years ago. Although its efficacy in patients with heart failure and atrial fibrillation is clear, its value in patients with heart failure and sinus rhythm has often been questioned. In the 1980s, reports of some large-scale trials indicated that digoxin, with or without vasodilators or angiotensin-converting enzyme inhibitors, reduced signs and symptoms of congestive heart failure and improved exercise tolerance. This beneficial influence was mainly found in patients with more advanced heart failure and dilated ventricles, whereas the effect in those with mild disease appeared to be less pronounced. In the last few years, new data have shown that digoxin may also have clinical value in mild heart failure, either when used in combination with other drugs or when administered alone. As neurohumoral activation has increasingly been recognized to be a contributing factor in the disease progression of chronic heart failure, the modulating effects of digoxin on neurohumoral and autonomic status have received more attention. Also, there is evidence that relatively low doses of digoxin may be at least as effective as higher doses and have a lower incidence of side effects. Further, the recognition that the use of digoxin too early after myocardial infarction may be harmful and the development of other drugs, in particular angiotensin-converting enzyme inhibitors, have obviously changed the place of digoxin in the treatment of chronic heart failure. The large-scale survival trial by the Digitalis Investigators Group (DIG), whose preliminary results have recently been presented, has shown that although digoxin has a neutral effect on total mortality during long-term treatment, it reduces the number of hospital admissions and deaths due to worsening heart failure. The potentially new features of the old drug digoxin are discussed in this review.

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Ever since 1785, when William Withering (1) described the use of digitalis in patients with heart failure, this drug has been subject to debate and controversy (2–5). Although the value of digoxin in patients with heart failure who have atrial fibrillation has generally been recognized, its efficacy in those who have sinus rhythm has often been questioned. Nevertheless, the drug has continued to be widely used in the United States (2) and Europe, possibly because "old habits die slowly" (5). Renewed scientific interest emerged, however, when it was found that digitalis had a significant effect on neurohumoral activation and autonomic function in patients with heart failure (6), an effect that may explain some of its (alleged) favorable properties in this syndrome (7).

During the last decade, the popularity of digoxin has again increased. This has been partly due to the results of three large scale trials published at the end of the 1980s that did not primarily investigate digoxin itself but used it as a reference drug (8–10). In these three placebo-controlled trials, which studied >300 patients taking digoxin, the drug was found to cause a statistically significant improvement in exercise time (10) and left ventricular ejection fraction (8,10) and to decrease signs and symptoms of heart failure (9). In the beginning of the 1990s, two other placebo-controlled studies (11,12) showed a beneficial effect of digoxin on exercise capacity, ejection fraction and clinical variables, both in the presence (11) and in the absence (12) of concomitant angiotensin-converting enzyme therapy. However, both studies had a withdrawal design, and the question remains whether their results can be applied to patients in whom digoxin treatment is initiated (3,13).

In recent years, evidence has accumulated that disease progression in chronic heart failure is related not only to hemodynamic but also to neurohumoral factors (14). As a consequence, it has become clear that a pronounced beneficial hemodynamic effect of a drug is not necessarily related to a decrease in morbidity and mortality. The autonomic and neurohumoral effects of a drug may in this respect be more predictive (15), an observation that has also led to renewed interest in digoxin. Other new developments, such as the successful use of lower doses of digoxin, have also contributed to this revived interest. In this review, we discuss recent data on digoxin and place these data against the background of the traditional view of digoxin in the treatment of heart failure. Finally, we briefly discuss the recently presented results of the

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Abbreviations and Acronyms
DIG = Digitalis Investigators Group
DIMT = Dutch Ibopamine Multicenter Trial

large mortality trial carried out by the Digitalis Investigators Group: the DIG study.*

Importance of Digitalis-Induced Neurohumoral Modulation

Traditionally, heart failure has been considered a hemodynamic disorder and, as a result, drug treatment has primarily attempted to correct hemodynamic abnormalities (14,17). However, the concept of the pathophysiology of heart failure has changed during the last 10 years, and recent data strongly support an important role for neurohumoral modulation or inhibition in its treatment. Moreover, the favorable long-term effects of some drugs in heart failure, particularly angiotensin-converting enzyme inhibitors, have for an important part been attributed to their neurohumoral effects (18,19).

In the past, digitalis has been considered a pure positive inotropic agent. As a result, the disappointing results of some large scale trials with positive inotropic agents in the 1980s (20) led to concern that similar disappointing effects could be expected with digoxin (21), particularly because the deleterious effects of inotropic drugs appear to be independent of their mechanism of action (22). In recent years, evidence has emerged that digoxin exerts its inotropic effects mainly at higher doses; at lower doses little inotropic action but more pronounced neurohumoral effects are observed (23).

Several studies now available have evaluated the neurohumoral and autonomic effects of digoxin. Digitalis appears to modulate sympathetic tone (7) in a manner similar to that of its hemodynamic effects, which differ between healthy volunteers and patients with heart failure (24). In heart failure, it will, in general, have a sympathoinhibitory effect, depending on the severity of the disease (25) and on the dose used (23,26). There are several potential explanations for the neuroendocrine inhibitory effects of digitalis in heart failure (6,7), but the observed improvement or normalization of impaired baroreceptor-mediated mechanisms appears to play an important role (26,27), although not all studies (28) support this concept. A reduction of sympathetic tone in heart failure has been demonstrated by directly measuring efferent sympathetic nerve activity in skeletal muscle (6) or, more easily, by determining plasma norepinephrine concentrations. In two older studies (29,30) it was shown that digoxin immediately reduced plasma norepinephrine concentrations in patients with heart failure. In the recently published Dutch Ibopamine Multicenter Trial (DIMT), we (25) showed that this effect was sustained over 6 months of treatment. In a further analysis of these data (31), this effect was even present in patients with very mild heart failure who received no other drug treatment for their disease. Digoxin may also lower plasma renin levels (25,29,32). This reduction may be a direct renal effect (33) or secondary to inhibition of sympathetic activity (34) or caused by activation of atrial natriuretic factor (33,35), although the latter effect is rather small in humans (36). Plasma aldosterone has been reported (27) to decrease with digoxin, but this effect is not very pronounced (25).

In addition to these neurohormonal actions, effects of digitalis on both cardiopulmonary and arterial baroreceptor function in humans have long been recognized (7,26,37–41). Because baroreceptors modulate sympathetic and parasympathetic (or vagal) activity as a result of stretch of the mechanoreceptors, neurohormonal changes measured in plasma and muscle, as described earlier, are directly related to the effects of digitalis on baroreceptors (42). Why baroreceptor reflex function is impaired in heart failure and how digitalis improves baroreceptor function in this syndrome have also not been fully elucidated. Several possibilities to explain the latter have been suggested, including 1) a direct receptor effect, 2) an increase in blood pressure, and 3) inhibition of excessive activation of the sodium-potassium adenosine triphosphatase pump (6,7).

In recent years, analysis of heart rate variability has become a valuable tool to examine (noninvasively) autonomic function in heart failure, and changes in heart rate variability indexes may have some predictive value with regard to the long-term efficacy of drugs in this syndrome (15). Recently, three studies have examined the effects of digoxin on heart rate variability indexes, both in patients with heart failure (43,44) and in normal subjects (45). Krum et al. (43) studied patients with moderate heart failure, most of whom received background treatment with converting enzyme inhibitors. After 4 to 8 weeks of treatment with rather low doses of digoxin, time domain variables increased significantly and frequency domain variables also improved toward normal, indicating that parasympathetic activity increased substantially whereas sympathetic activity decreased. In another study, Brouwer et al. (44) examined patients with mild heart failure who had been receiving either low dose diuretic drugs alone or no medication for heart failure. After 3 months, heart rate variability indexes deteriorated slightly in the placebo group but improved significantly in the digoxin group compared with values in the patients receiving placebo. These observations (44) were essentially the same as those made by Krum et al. (43), although the effect of digoxin was less pronounced (Fig. 1). Even in normal subjects (45), digoxin was found to significantly affect heart rate variability measures, particularly the indexes of vagal modulation. In line with the observed effects on sympathovagal balance, digoxin may partly restore the impaired circadian pattern of heart rate variability (44) that is observed in patients with heart failure (46). This effect appears to be related to changes in the circadian pattern of circulating plasma norepinephrine after digoxin administration. This finding obviously raises new questions with regard to the well known circadian pattern in the

*Gorlin R, Garg R. The effects of digitalis on mortality and hospitalizations in patients with heart failure. Presented at the 45th Annual Scientific Session of the American College of Cardiology, Orlando, Florida, March 1996.

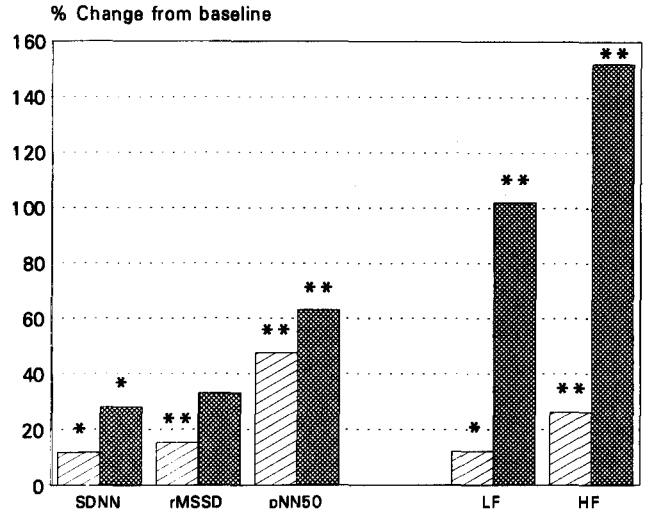

Figure 1. Effects of digoxin on time domain and frequency domain heart rate variability indexes. Changes are expressed as percent of baseline value. Patients with heart failure not treated with angiotensin-converting enzyme inhibitors who generally had mild heart failure (mean left ventricular ejection fraction 0.28 [**hatched bars**]; data from Brouwer et al. [44]) are compared with patients who were treated with these drugs and had more advanced or moderate heart failure (mean ejection fraction 0.22 [**cross-hatched bars**]; data from Krum et al. [43]) *$p < 0.05$; *$p < 0.005$. HF = high frequency power (0.15 to 0.40 Hz) (ms^2); LF = low frequency power (0.04 to 0.15 Hz) (ms^2); pNN50 = percent of adjacent normal RR intervals (%); rMSSD = root mean square of successive difference (ms); SDNN = 24-h standard deviation of all normal to normal RR intervals (ms).

incidence of certain cardiovascular disorders, including sudden death.

Digoxin May Be Effective in Both Mild and Advanced Heart Failure

It has always been assumed that the favorable effect of digoxin is more pronounced in—or, rather, would largely be restricted to—patients with moderate to severe heart failure (47–56), and this assumption was confirmed in a meta-analysis of digoxin in 1990 (57). However, in a subsequent review, Gheorghiade and Zarowitz (58) pointed out that evidence existed that the drug might also be effective in less advanced heart failure, a finding supported by recent data from our group (25,31) and from others (59,60). In the DIMT study (25), patients with predominantly mild heart failure were randomized to treatment with digoxin (n = 55), ibopamine (n = 53) or placebo (n = 53). The results showed that digoxin significantly improved exercise time over that achieved with placebo after 6 months. Subanalysis of the data indicated that the drug was indeed relatively more effective in patients with more advanced disease (25). Nevertheless, digoxin was also effective in patients with mild disease, and when its effects as monotherapy were analyzed (in the 64 patients [40%] who did not receive diuretic drugs at baseline), digoxin was found to be more effective than placebo because it significantly improved exercise time and reduced plasma neurohormones after 6 months (Fig. 2) (31). These findings are in agreement with data from two other recent studies in patients with mild heart failure in whom the effect of digoxin as monotherapy was evaluated (59,60). In the German-Austrian Captopril and Digoxin Study (CADS), Just et al. (59) studied 222 patients who were randomized to receive digoxin (n = 66), captopril (n = 63) or placebo (n = 67) and were followed up for 2 years. Digoxin significantly improved quality of life and decreased clinical symptoms in comparison with placebo, and more side-effects were observed with captopril than with digoxin. In another study, Kleber and Thyroff-Friesinger (60) studied 60 patients who were randomized to receive digoxin (n = 22), ibopamine (n = 18) or placebo (n = 20), and these patients were followed up for only 4 weeks. During that study there were no treatment failures in the group receiving digoxin, and quality of life improved in 21 of the 22 patients. In general, digoxin was comparable to ibopamine and significantly more effective than placebo.

Digoxin Dosage: Higher Is Not Necessarily Better

Another important issue in the use of digitalis has been establishment of the optimal dose (23,61). In the past, when the inotropic effect of the drug was considered of primary importance, relatively high doses were generally used. How-

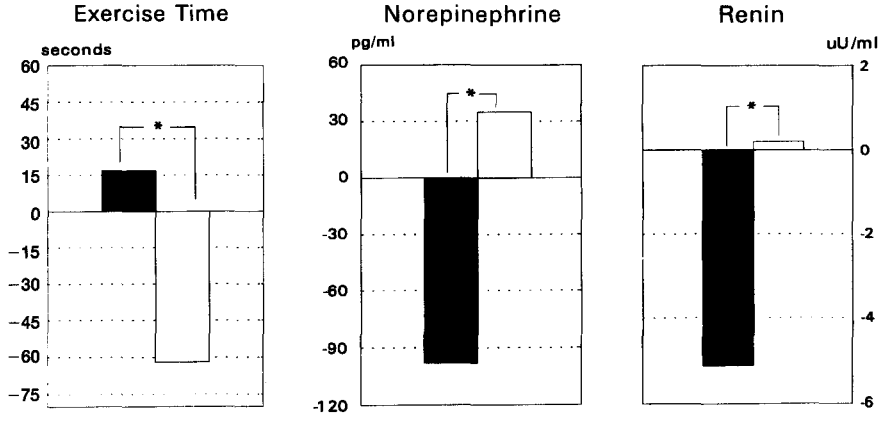

Figure 2. Effects of 6 months of monotherapy with digoxin (n = 22, **solid bars**) or placebo (n = 20, **open bars**) on exercise time, plasma norepinephrine and plasma renin in patients with mild heart failure. *$p < 0.05$. Adapted from van Veldhuisen et al. (31).

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ever, as pointed out earlier, it has gradually become clear that lower doses of digoxin may also be effective and result in less toxicity (23). In an early postinfarction trial (62), serum digoxin concentrations were associated with an adverse prognosis, but this association was no longer statistically significant after adjustment for other risk factors. However, in a subanalysis of a large heart failure trial (Prospective Randomized Milrinone Survival Evaluation [PROMISE] study) (63), high serum digoxin levels (>1.1 ng/ml) were found to be independently related to an adverse prognosis. Some recent "positive" findings (25,43,44), such as favorable effects of digoxin on plasma neurohormones and heart rate variability, were observed in patients who were receiving low doses of the drug. In a recent study (64), when the daily dose of digoxin was increased from 0.20 ± 0.1 mg/day to 0.39 ± 0.1 mg/day (which corresponded to serum levels of 0.7 ± 0.2 ng/ml and 1.2 ± 0.4 ng/ml, respectively), left ventricular ejection fraction increased, but neurohormones did not decrease. Indeed, increasing the digoxin dose to these serum levels may improve left ventricular (systolic) function (64,65), but lower doses may already be effective in the suppression of neurohormones, an observation that agrees with earlier evidence that low doses of digitalis primarily exert neurohumoral and autonomic effects, whereas high or higher doses mainly have inotropic action (23). Combined data from the Prospective Randomized Study of ventricular failure and the Efficacy of Digoxin (PROVED) and Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme (RADIANCE) trials (66) and from others (67) suggest that trying to push the digoxin dose to serum levels above ±1.2 ng/ml may be questionable, whereas increasing the dose to levels 1.5 to 2.0 ng/ml is probably unwanted (51). However, it is difficult to compare serum digoxin concentrations among studies because there is no standardized time after dosing for obtaining serum levels, and several other technical problems may cause additional bias (67).

If lower doses of digoxin are used, the number of side effects, including serious adverse events, such as arrhythmias, will obviously decrease (68,69). This is particularly true in elderly patients, because the incidence of digitalis toxicity is high and recognition of toxicity may be particularly difficult in this group (70,71). Moreover, very low doses of the drug may already be effective in these patients (72).

Digoxin Should Be Given With Caution After Myocardial Infarction

Several large retrospective studies have examined the effect of digitalis in acute myocardial infarction (62,73,74). Although these studies generally show that patients treated with digitalis fared worse than those who were not, their findings are limited by the fact that most patients who were taking digitalis were doing so because they suffered from more severely impaired left ventricular function (75). Nevertheless, a recent large scale study (76) that corrected for all confounding factors (such as left ventricular function) also found a relative risk of 1.8 in multivariate analysis associated with digoxin use.

Unfortunately, only a few small prospective studies on the value of digoxin after acute myocardial infarction are available. In two older studies, digoxin was found not to affect preload or afterload (77) or to improve hemodynamics (78). In another study (79), digoxin improved hemodynamics but only in patients with heart failure. In a recent investigation (80), digoxin had an adverse effect on ventricular remodeling after anterior myocardial infarction, but it increased ejection fraction. This finding has been reported before (81), but its clinical relevance is unclear.

There are several reasons why digitalis might not be beneficial in acute myocardial infarction (82–84). It may increase myocardial oxygen consumption (49) by augmenting contractility (85), by increasing intramyocardial tension and by inducing peripheral or coronary (86) vasoconstriction. Also, it may provoke or aggravate myocardial ischemia, leading to ventricular arrhythmias and death, and it may increase infarct size (87). Because myocardial stunning or hibernation may be present for weeks after infarction, use of digoxin should in general be avoided in the (sub)acute phase after infarction, unless there is strong indication for its administration such as rapid atrial fibrillation. In the past, heart failure in the acute phase of myocardial infarction was often treated with digoxin (82,83), but this is no longer the general practice. One factor may be that digoxin may aggravate the clinical condition in the setting of cardiogenic shock (88) and, therefore, dobutamine or dopamine is now often used instead. In addition, the positive results of recent large scale trials with angiotensin-converting enzyme inhibitors in this setting (89,90) have also played a role in this change.

Other Possible Factors in the Declining Role of Digoxin in Heart Failure

Other factors may also have been involved in the declining role of digoxin in heart failure in the late 1970s and early 1980s. At that time, angiotensin-converting enzyme inhibitors became available for the treatment of heart failure. These agents were soon found to significantly reduce morbidity and mortality, both in severe (91), but also in less advanced (92,93) heart failure, and they are currently the cornerstone of heart failure treatment. In many patients with mild to moderate heart failure, these drugs, rather than digoxin (94), are used in combination with diuretic drugs, and many physicians are now even inclined to initiate medical treatment with these drugs alone, as monotherapy. Because only angiotensin-converting enzyme inhibitors have been shown to favorably affect the natural history of heart failure, it has been stated (95) that digoxin should be reserved for patients who remain symptomatic after treatment with angiotensin-converting enzyme inhibitors and diuretic drugs.

Another important, often neglected factor is the fact that digoxin is a very inexpensive drug. As a result, pharmaceutical companies have not been enthusiastic to start major trials with this drug. Thus, the large scale digoxin survival trial, the DIG study, is sponsored by the National Institutes of Health in

conjunction with Department of Veterans Affairs Cooperative Studies Program (16,96). It is ironic, as mentioned earlier, that many important data on digoxin have been gained from studies that were primarily aimed at investigating new compounds and were sponsored by the companies manufacturing these compounds (8,10,25,59). The low cost of digoxin obviously has a positive side, and a recent health care analysis (97) showed that discontinuation of digoxin in patients with stable heart failure leads to increased economic costs.

Effects of Digoxin on Mortality in Patients With Heart Failure

Until recently, only retrospective and uncontrolled data were available concerning the effect of digoxin on mortality in patients with chronic heart failure. For this reason, the large scale DIG trial was designed and sponsored by the National Institutes of Health in conjunction with the Department of Veterans Affairs Cooperative Studies Program (16,96,98). In this double-blind, parallel group comparison, patients with heart failure and sinus rhythm were randomized to receive digoxin or placebo in addition to other medication. Patients were required to have current or past evidence of signs and symptoms of heart failure and a left ventricular ejection fraction ≤ 0.45. In a parallel, separate smaller study ($\pm 1{,}000$ patients) the effects in those with an ejection fraction >0.45 were studied. The primary end point of the study was the effect of digitalis on total mortality; secondary end points included a (first) hospital admission for worsening heart failure or other causes, cardiovascular mortality, death due to worsening heart failure and (presumed) arrhythmias, and effects on quality of life. The dose of digoxin during the study was based on an algorithm that included age, gender, weight and renal function. Recruitment for the study started in early 1991, and by the end of 1995, almost 8,000 patients had been enrolled in the United States and Canada.

Preliminary analysis of the results (16) showed that digoxin had no effect on total mortality during a mean follow-up period of >3 years. However, the number of hospital admissions and the number of deaths due to worsening heart failure were significantly reduced by digoxin, whereas the incidence of presumed arrhythmic deaths and deaths due to myocardial infarction tended to increase. Although there was some suggestion that the reduction in risk of worsening heart failure achieved by digoxin was most pronounced in patients with a lower ejection fraction, the reduction was not significantly different between patients with relatively preserved and patients with relatively impaired left ventricular function.

This latter observation would support the hypothesis that digoxin might be effective not only in advanced, but also in milder stages of heart failure, as discussed earlier. The majority of patients were taking 0.25 mg/day of digoxin, and almost 30% of patients had a serum digoxin level >1.0 ng/ml. However, no data were presented concerning the influence of digoxin dose or serum levels on clinical outcome. Results of quality of life assessment were not yet available.

Summary

The use of digoxin in patients with heart failure and sinus rhythm has been controversial for >200 years. Many of the positive data on digoxin have been gained from withdrawal trials and have therefore often been criticized. Several prospective, double-blind randomized studies published in the last few years have shed new light on the value and place of digoxin in the treatment of patients with heart failure and sinus rhythm. Furthermore, preliminary results of DIG, the large scale mortality trial, have yielded important new information about this drug. The main finding from that study to date is that digoxin has a neutral effect on total mortality in patients with heart failure. However, the drug has significantly reduced the number of deaths due to worsening heart failure and related hospital admissions, data that suggest that it may slow progression of the disease. Although the final data have not been published, the results do not clearly point in one direction, and it is therefore likely that the controversy regarding this drug will continue. From these newer data and from other developments with regard to the insights into the pathophysiology and treatment of heart failure, several issues concerning the value and use of digoxin have become clear.

1) In light of the generally accepted importance of neurohumoral activation in the pathophysiology of heart failure, the recently recognized positive neurohumoral effects of digoxin (including its influence on baroreceptor function and heart rate variability) seem promising. 2) Although digoxin appears to be most effective in advanced heart failure, several new studies show that it may also be of value in patients with milder stages of the disease. In the latter, however, it is by definition more difficult to show a significant drug effect, and studies in this patient group should thus be conducted with larger sample sizes and a longer follow-up period, as has been done with angiotensin-converting enzyme inhibitors (99). 3) Relatively high doses of digoxin have traditionally been used, but recent data suggest that lower doses may be effective as well. When lower doses are used, fewer side effects will occur, and the subjective well-being of the patient may improve. 4) Patients with a new or fairly recent myocardial infarction should, in general, probably not be treated with digoxin, and the drug should be used with some caution in patients who have heart failure after infarction. Because digoxin has often been administered to these patients in the past, the negative results of some reported trials may be partly explained by this factor. Finally, other factors may be involved in the declining role of digoxin in heart failure, including the increased use of angiotensin-converting enzyme inhibitors, and the low cost of digoxin, which makes research with this compound less attractive to pharmaceutical companies.

References

1. Withering W. An Account of the Foxglove, and some of its Medical Uses: with Practical Remarks on Dropsy, and other Diseases. London: GGJ and J Robinson, 1785:232–52.
2. Gheorghiade M. A Symposium: Management of heart failure in the 1990s: a

reassessment of the role of digoxin therapy. Introduction. Am J Cardiol 1992;69:1G–3G.
3. De Bono D. Digoxin in eurhythmic heart failure: PROVED or "not proven"? [editorial]. Lancet 1994;343:128–9.
4. Parmley WW. Should digoxin be the drug of choice after diuretics in chronic congestive heart failure? Introduction. J Am Coll Cardiol 1988;12:265–7.
5. Poole-Wilson PA. Digitalis: dead or alive? Cardiology 1988;75(Suppl 1): 103–9.
6. Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienzle MG. Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. Circulation 1989;80: 65–77.
7. Gheorghiade M, Ferguson D. Digoxin. A neurohumoral modulator in heart failure? Circulation 1989;84:2181–6.
8. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539–44.
9. The German and Austrian Xamoterol Study Group. Double-blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. Lancet 1988;1:489–93.
10. DiBianco R, Shabetai R, Kostuk W, et al. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989;320:677–83.
11. Packer M, Gheorghiade M, Young JB, et al. for the RADIANCE Study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. N Engl J Med 1993;329:1–7.
12. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK, on behalf of the PROVED Investigative Group. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED Trial. J Am Coll Cardiol 1993;22:955–62.
13. Poole-Wilson PA. Digoxin withdrawal in patients with heart failure [letter]. J Am Coll Cardiol 1994;24:578–82.
14. Packer M. The neurohumoral hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248–54.
15. Tuininga YS, Van Veldhuisen DJ, Brouwer J, et al. Heart rate variability in left ventricular dysfunction and heart failure: effects and implications of drug treatment. Br Heart J 1994;72:509–13.
16. Cohen JN. Management of chronic heart failure. N Engl J Med 1996;335: 490–8.
17. Remme WJ. Therapeutic strategies and neurohumoral control in heart failure. Eur Heart J 1994;15 Suppl D:129–38.
18. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A, for the V-HeFT VA Cooperative Studies Group. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. Circulation 1993;87 Suppl VI:VI-40–8.
19. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L, for the CONSENSUS Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990;82:1730–6.
20. Cohn JN. Inotropic therapy for heart failure: paradise postponed. N Engl J Med 1989;320:729–31.
21. Remme WJ. Inotropic agents for heart failure: what if digoxin increases mortality? Br Heart J 1994;72 Suppl:92–9.
22. Katz AM. Potential deleterious effects of inotropic agents in the therapy of chronic heart failure. Circulation 1986;73 Suppl III:III-184–8.
23. Packer M. The development of positive inotropic agents for chronic heart failure: how have we gone astray? J Am Coll Cardiol 1993;22 Suppl A:119A–26A.
24. Mason DT, Braunwald E. Studies on digitalis: X. Effects of ouabain on forearm vascular resistance and venous tone in normal subjects and patients with heart failure. J Clin Invest 1964;43:532–43.
25. van Veldhuisen DJ, Man in 't Veld AJ, Dunselman PHJM, et al. Double-blind, placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: Results of the Dutch Ibopamine Multicenter Trial (DIMT). J Am Coll Cardiol 1993;22:1564–73.
26. Watanabe AM. Digitalis and the autonomic nervous system. J Am Coll Cardiol 1985;5 Suppl A:35A–42A.
27. Ferguson DW. Digitalis and neurohormonal abnormalities in heart failure and implications for therapy. Am J Cardiol 1992;69:24G–33G.
28. Goldsmith SR, Simon AB, Miller E. Effect of digitalis on norepinephrine kinetics in congestive heart failure. J Am Coll Cardiol 1992;20:858–63.
29. Ribner HS, Plucinski DA, Hsieh AM, et al. Acute effects of digoxin on total systemic vascular resistance in congestive heart failure due to dilated cardiomyopathy: a hemodynamic-hormonal study. Am J Cardiol 1985;56: 896–904.
30. Gheorghiade M, Hall V, Lakier JB, Goldstein S. Comparative hemodynamic and neurohormonal effects of intravenous captopril and digoxin and their combinations in patients with heart failure. J Am Coll Cardiol 1989;13:134–42.
31. van Veldhuisen DJ, Brouwer J, Man in 't Veld AJ, Dunselman PHJM, Boomsma F, Lie KI. Progression of mild untreated heart failure during 6 months follow-up and clinical and neurohumoral effects of ibopamine and digoxin as monotherapy. Am J Cardiol 1995;75:796–800.
32. Covit AB, Schaer GL, Sealy JE, Laragh JH, Cody RJ. Suppression of the renin-angiotensin system by intravenous digoxin in chronic congestive heart failure. Am J Med 1983;75:445–7.
33. Lloyd MA, Sandberg SM, Edwards BS. Role of renal Na^+, K^+-ATP-ase in the regulation of sodium excretion under normal conditions and in acute congestive heart failure. Circulation 1992;85:1912–7.
34. Thames MD. Acethylstrophantidin-induced reflex inhibition of canine renal sympathetic nerve activity mediated by cardiac receptors with vagal afferents. Circ Res 1979;44:8–15.
35. Bloch KD, Zmir N, Lichtstein D, Seidman CE, Seidman JG. Ouabain induces secretion of pro-atrial natriuretic factor in rat cardiac cardiocytes. Am J Physiol 1988;255:E383–7.
36. Gheorghiade M, Hall VB, Fenn NM, Goldstein S. Chronic effects of digoxin withdrawal on neurohormones in patients with stable heart failure treated with converting enzyme inhibitors [abstract]. Eur Heart J 1993;14 Abstract Suppl:131.
37. Gillis RA, Quest JA. The role of the nervous system in the cardiovascular effects of digitalis. Pharmacol Rev 1980;31:19–97.
38. Ferrari A, Gregorini L, Ferrari MC, Preti L, Mancia G. Digitalis and baroreceptor reflexes in man. Circulation 1981;63:279–85.
39. Ferrari A, Bonazzi O, Gregorini L, Gardumi M, Perondi R, Mancia G. Modification of the baroreceptor control of atrioventricular conduction induced by digitalis in man. Cardiovasc Res 1983;17:633–41.
40. Ferguson DW, Abboud FM, Mark AL. Selective impairment of baroreflex-mediated vasoconstrictor responses in patients with ventricular dysfunction. Circulation 1984;69:451–60.
41. Imamura T, Takeshita A, Ashihara T, Yamamoto K, Hoka S, Nakamura M. Digitalis-induced augmentation of cardiopulmonary baroreflex control of forearm vascular resistance. Circulation 1985;71:11–6.
42. Hirsch AT, Dzau VJ, Creager MA. Baroreceptor function in congestive heart failure: effect on neurohumoral activation and regional vascular resistance. Circulation 1987;75 Suppl IV:IV-36–48.
43. Krum H, Bigger JT, Goldsmith RL, Packer M. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. J Am Coll Cardiol 1995;25:289–94.
44. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, et al. Heart rate variability in patients with mild to moderate heart failure: effects of neurohumoral modulation by digoxin and ibopamine. J Am Coll Cardiol 1995;26:983–90.
45. Kaufman ES, Bosner MS, Bigger JT, et al. Effects of digoxin and enalapril on heart rate variability and response to head-up tilt in normal subjects. Am J Cardiol 1993;72:95–9.
46. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, Dunselman PHJM, Haaksma J, Lie KI. Circadian pattern of heart rate variability in heart failure is progressively disturbed with increasing neurohumoral activation [abstract]. J Am Coll Cardiol 1994;23 Suppl A:392A.
47. Kimmelstiel C, Benotti JR. How effective is digitalis in the treatment of congestive heart failure? Am Heart J 1988;116:1063–70.
48. Parmley WW. Pathophysiology and current therapy of congestive heart failure. J Am Coll Cardiol 1989;13:771–85.
49. Smith TW. Digitalis. Mechanisms of action and clinical use. N Engl J Med 1988;318:358–65.
50. Lee DC, Johnson RA, Bingham JB, et al. Heart failure in outpatients: a randomized trial of digoxin versus placebo. N Engl J Med 1982;306:4–9.
51. Guyatt GH, Sullivan MJ, Fallen EL, et al. A controlled trial of digoxin in congestive heart failure. Am J Cardiol 1988;61:371–5.
52. Arnold SB, Byrd RC, Meister W, et al. Long-term digitalis therapy improves left ventricular function in heart failure. N Engl J Med 1980;303:1443–8.

53. Gheorghiade M, StClair J, StClair C, Beller GA. Hemodynamic effects of intravenous digoxin in patients with severe heart failure initially treated with diuretics and vasodilators. J Am Coll Cardiol 1987;9:849–57.
54. Fleg JL, Gottlieb SH, Lakatta EG. Is digoxin really important in treatment of compensated heart failure? A placebo-controlled crossover study in patients with sinus rhythm. Am J Med 1982;73:244–50.
55. Fleg JH, Rothfeld B, Gottlieb SH, Wright J. Effects of maintenance digoxin on aerobic performance and exercise left ventricular function in mild to moderate heart failure due to coronary artery disease: a randomized, placebo-controlled, crossover trial. J Am Coll Cardiol 1991;17:743–51.
56. Kelly RA, Smith TW. Digoxin in heart failure: implications of recent trials. J Am Coll Cardiol 1993;22 Suppl A:107A–12A.
57. Jaeschke R, Oxman AD, Guyatt GH. To what extent do congestive heart failure patients in sinus rhythm benefit from digoxin therapy? A systemic overview and meta-analysis. Am J Med 1990;88:279–86.
58. Gheorghiade M, Zarowitz BJ. Review of randomized trials of digoxin therapy in patients with chronic heart failure. Am J Cardiol 1992;69:48G–63G.
59. Just H, Drexler H, Taylor SH, Siegrist J, Schulgen G, Schumacher M, for the CADS Study Group. Captopril versus digoxin in patients with coronary artery disease and mild heart failure. A prospective, double-blind, placebo-controlled multicenter study. Herz 1993;18 Suppl 1:436–43.
60. Kleber FX, Thyroff-Friesinger U. Ibopamine versus digoxin in the treatment of mild congestive heart failure. Cardiology 1990;77 Suppl 5:75–80.
61. Tauke J, Goldstein S, Gheorghiade M. Digoxin for chronic heart failure: a review of the randomized controlled trials with special attention to the PROVED and RADIANCE Trials. Prog Cardiovasc Dis 1994;37:49–58.
62. Bigger JT, Fleiss JL, Rolnitzky LM, Merab JP, Ferrick KJ. Effect of digitalis on survival after myocardial infarction. Am J Cardiol 1985;55:623–30.
63. Mancini DM, Benotti JR, Elkayam U, et al., and the PROMISE Investigators and Coordinators. Antiarrhythmic drug use and high serum levels of digoxin are independent adverse prognostic factors in patients with chronic heart failure [abstract]. Circulation 1991;84 Suppl II:II–243.
64. Gheorghiade M, Hall VB, Jacobson G, Alam M, Rosman H, Goldstein S. Effects of increasing maintenance dose of digoxin on left ventricular function and neurohormones in patients with chronic heart failure treated with diuretics and angiotensin-converting enzyme inhibitors. Circulation 1995;92: 1801–7.
65. Hoeschen RJ, Cuddy TE. Dose-response relation between therapeutic levels of serum digoxin and systolic time intervals. Am J Cardiol 1975;35:469–72.
66. Young JB, Gheorghiade M, Packer M, et al., on behalf of the PROVED and RADIANCE Investigators. Are low serum levels of digoxin effective in chronic heart failure? Evidence challenging the accepted guidelines for a therapeutic serum level of the drug [abstract]. J Am Coll Cardiol 1993;21 Suppl A:378A.
67. Lewis RP. Clinical use of serum digoxin concentrations. Am J Cardiol 1992;69:97G–107G.
68. Smith TW, Antman EM, Friedman PL, Blatt CM, Marsch JD. Digitalis glycosides: mechanisms and manifestations of toxicity. Prog Cardiovasc Dis 1984;27:21–41.
69. Fisch C, Knoebel SB. Digitalis cardiotoxicity. J Am Coll Cardiol 1985;5:91A–8A.
70. Warren JL, McBean AM, Hass SL, Babish JD. Hospitalizations with adverse events caused by digitalis therapy among elderly Medicare beneficiaries. Arch Intern Med 1994;154:1482–7.
71. Kelly RA, Smith TW. Recognition and management of digitalis toxicity. Am J Cardiol 1992;69:108G–19G.
72. Ware JA, Snow E, Luchi JM, Luchi RJ. Effect of digoxin on ejection fraction in elderly patients with congestive heart failure. J Am Geriatr Soc 1984;32: 631–5.
73. Moss AJ, Davis HT, Conard DL, DeCamilla JJ, Odoroff CL. Digitalis-associated cardiac mortality after myocardial infarction. Circulation 1981;64: 1150–6.
74. Byington R, Goldstein S, for the BHAT Research Group. Association of digitalis therapy with mortality in survivors of acute myocardial infaction: observations in the Beta-blocker Heart Attack Trial. J Am Coll Cardiol 1985;6:976–82.
75. Yusuf S, Wittes J, Bailey K, Furberg C. Digitalis—a new controversy regarding an old drug. The pitfalls of inappropriate methods. Circulation 1986;73:14–8.
76. Køber L, Torp-Pedersen C, Gadsbøll N, Hildebrandt P, Høilund-Carlsen PF. Is digoxin an independent risk factor for long-term mortality after acute myocardial infarction? Eur Heart J 1994;15:382–8.
77. Goldstein RA, Passamani ER, Roberts R. A comparison of digoxin and dobutamine in patients with acute infarction and cardiac failure. N Engl J Med 1980;303:846–50.
78. Forrester J, Bezdek W, Chatterjee K, et al. Hemodynamic effects of digitalis in acute myocardial infarction. Ann Intern Med 1972;76:863–4.
79. Lipp H, Denes P, Gambetta M, et al. Hemodynamic response to acute intravenous digoxin in patients with recent myocardial infarction and coronary insufficiency with and without heart failure. Chest 1972;63:862–7.
80. Bonaduce D, Petretta M, Arrichiello P, et al. Effects of captopril treatment on left ventricular remodeling and function after anterior myocardial infarction: comparison with digitalis. J Am Coll Cardiol 1992;19:858–63.
81. Morrison J, Caromilas J, Robbins M, et al. Digitalis and myocardial infarction in man. Circulation 1980;62:8–16.
82. Marcus FI. Use of digitalis in acute myocardial infarction. Circulation 1980;62:17–9.
83. Rahimtoola SH, Gunnar RM. Digitalis in acute myocardial infarction: help or hazard? Ann Intern Med 1975;82:234–40.
84. Karliner JS, Braunwald E. Present status of digitalis treatment of acute myocardial infarction patients. Circulation 1972;45:891–6.
85. Covell JW, Braunwald E, Ross J, Sonnenblick E. Studies on digitalis XVI. Effects on myocardial oxygen consumption. J Clin Invest 1966;45:1535–42.
86. Gross GJ, Waltier DC, Hardman HF, Somani P. The effect of ouabain on nutritional circulation and regional myocardial blood flow. Am Heart J 1977;93:487–95.
87. Lynch JJ, Simpson PJ, Gallagher KP, McClanahan TB, Lee KA, Lucchesi BR. Increase in experimental infarct size with digoxin in a canine model of myocardial ischemia-reperfusion injury. Am Heart J 1988;115:1171–82.
88. Cohn JN, Tristani FE, Khatri IM. Cardiac and peripheral vascular effects of digitalis in clinical cardiogenic shock. Am Heart J 1969;78:318–330.
89. Pfeffer MA, Braunwald E, Moye LA, et al. The effect of captopril on mortality in patients with left ventricular dysfunction following myocardial infarction: results of the Survival and Ventricular Enlargement (SAVE) trial. N Engl J Med 1992;327:669–77.
90. Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821–7.
91. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.
92. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
93. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
94. Pitt B. Should digoxin be the drug of choice after diuretics in chronic congestive heart failure? Anatagonist's viewpoint. J Am Coll Cardiol 1988; 12:271–3.
95. Baker DW, Konstam MA, Bottorff M, Pitt B. Management of heart failure. I. Pharmacologic treatment. JAMA 1994;272:1361–6.
96. Yusuf S, Garg R, Held P, Gorlin R. Need for a large randomized trial to evaluate the effects of digitalis on morbidity and mortality in congestive heart failure. Am J Cardiol 1992;69:64G–70G.
97. Ward RE, Gheorghiade M, Young JB, Uretsky B. Economic outcomes of withdrawal digoxin therapy in adult patients with stable congestive heart failure. J Am Coll Cardiol 1995;26:93–101.
98. Uretsky BF. Digoxin in the treatment of patients with chronic heart failure. Its place in therapy. Drugs Aging 1995;7:1–9.
99. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.